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APPENDIX A

The inheritance and molecular genetics of von Willebrand's disease

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Introduction

Von Willebrand's disease (vWD) was first recognized as a separate entity in 1926 and described by Erik von Willebrand as hereditary pseudohaemophilia, a novel form of haemophilia. The features that distinguished vWD from classic haemophilia were a prolonged bleeding time, an autosomal inheritance pattern, and the occurrence of mucocutaneous haemorrhages rather than the predominant joint bleeds in haemophilia [1]. In 1971 the aetiologic difference between classic haemophilia (deficiency of factor VIII) and vWD was elucidated by the immunologic characterization of factor VIII-related antigen, now known as the antigen of von Willebrand factor (vWF) [2].

vWD is the most prevalent inherited bleeding disorder and it manifests a very heterogenous phenotypic expression with respect to the patients' clinical symptoms and laboratory data. The underlying genetic defects result in an abnormality of the activity or quantity of plasma and platelet vWF. Based on differences in clinical manifestations and structural defects of the vWF, the disease has been classified in many subtypes. This review will focus on the complicated inheritance and classification of several of the vWD subtypes and on the recent progress in the characterization of the molecular genetic defects that has contributed to a better understanding of the variable phenotypic expression.

Von Willebrand factor

vWF is an adhesive glycoprotein that circulates in plasma as very large multimers [3]. vWF is synthesized by endothelial cells [4] and megakaryocytes [5] and is both released through a regulated pathway after storage in the endothelial Weibel-Palade bodies [6] and platelet α-granules [7], and secreted constitutively by endothelial cells. vWF plays an essential role in primary haemostasis, because it mediates the interaction between platelets and subendothelium at sites of vascular damage (adhesion) and between platelets themselves (aggregation). After a conformational change, induced by interaction with the subendothelium or under high shear stress conditions, vWF binds to the platelet receptor glycoprotein Ib (GPIb) [8–10]. This leads to the subsequent expression of the platelet receptor glycoprotein IIb/IIIa (GPIIb/IIIa), which can then be complexed by vWF resulting in irreversible platelet adhesion and aggregation [9, 11]. Because vWF forms a non-covalently linked complex with coagulation factor VIII to stabilize it and protect it against degradation [12], decreased levels of vWF or reduced binding affinity for factor VIII may result in lower levels of factor VIII procoagulant activity (VIII:C) [12, 13].

Gene and biosynthesis of vWF

The amino acid sequence of vWF has been determined [14] and the cDNA encoding the vWF has been cloned [15–19]. The vWF gene, located on the short arm of chromosome 12 (12p 12-pter) [20, 21], is ~178 kilobases in length and contains 52 exons [22]. A partial, highly homologous, pseudogene is present on chromosome 22q11–13 [23].

vWF is synthesized as a single-chain precursor protein of 2813 amino acid residues and consists of four repeated domains (A–D) (Fig. 1) [18]. During post-translational modification in the rough endoplasmatic reticulum a 22 amino acids signal peptide is removed by cleavage [24], pro-vWF dimers are formed through covalent disulphide bridges between cysteine residues at the carboxy-terminus [25, 26] and initial glycosylation, required for normal dimerization, takes place [27, 28]. In the Golgi apparatus the pro-vWF dimers are assembled into multimers of very high molecular weight ($0.5–20 \times 10^6$ Da) through inter-chain disulphide pairing at the amino-terminus of the 2050 amino acids long mature vWF subunit [25, 27, 29]; concurrently the propeptide of 741 amino acids is cleaved off and final glycosylation takes place [24, 27].

Functional domains of vWF

A number of specific binding domains have been identified in the vWF (Fig. 1) that interact with other plasma proteins, platelet GPIb and GPIIb/IIIa receptors, and

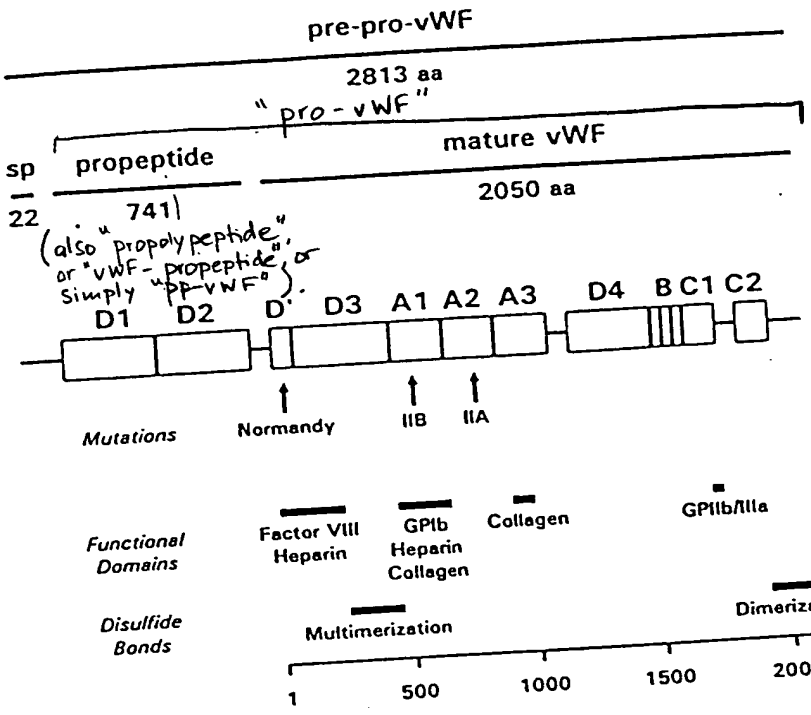

Fig. 1. Schematic representation of structural and functional features of vWF. At the top the single-chain pre-pro-vWF precursor protein of 2813 amino acids (aa) and the location of the signal peptide (sp), the vWF propeptide and the mature vWF subunit are shown. In the middle the repeated domains (A–D) are indicated as well as the location of regions with clustered vWD mutations (arrows). The diagram at the bottom represents the functional domains of vWF and the regions containing intersubunit disulphide bonds involved in dimerization and multimerization.

subendothelial components (recently reviewed by Ruggeri & Ware [30] and Meyer & Girma [9]). The domain that binds factor VIII has been localized in the first 272 amino acids of the mature vWF subunit [13,32] and a potential essential epitope has been mapped to a nonadecapeptide ranging from amino acid 78 to 96 [33].

The crucial role of vWF in platelet adhesion and aggregation is mediated through the binding of vWF to the platelet receptors GPIb and GPIIb/IIIa. The GPIb-binding domain has not been completely characterized, but several discontinuous sequences located in the A1 domain seem to be involved [34,35]. The Arg-Gly-Asp (RGD) sequence, which is also present in other adhesive proteins [36], at amino acids 1744–1746 of the mature vWF subunit is involved in the binding to the platelet receptor GPIIb/IIIa [37–42].

The interaction of vWF with subendothelium is probably mediated through binding to collagen type VI [43] and heparin-like molecules in the extracellular matrix. Binding domains for collagen types III, I and VI have been identified in the A1 and A3 domain of vWF [44–46]. Two heparin-binding sites have been documented [47–50].

Von Willebrand's disease

vWD is a congenital bleeding disorder caused by defects at the vWF gene locus. Other disorders which clinically resemble vWD have been documented. Platelet-type pseudo-vWD is caused by a defect of the platelet GPIb receptor [51–55]. Non-inherited abnormalities of the vWF as in acquired von Willebrand's syndrome occur in association with several disorders. These include lymphoproliferative disorders, such as monoclonal gammopathies and Waldenström's disease, autoimmune disorders, essential thrombocythaemia and hyperfibrinolysis [56–61].

Prevalence

The overall prevalence of vWD was estimated at ~1% in an epidemiological survey among school-children in the Veneto region of northern Italy [62]. Recently a similar prevalence (1.3%) was found in a multi-ethnic population [63]. If only the treated patients are included, the prevalence is much lower and ranges from 6.5 to 30.7 per million, with the highest prevalence in the Scandinavian countries [64].

Clinical symptoms

The bleeding symptoms in vWD are usually mild. The most prominent features reflect a disrupted primary haemostasis: easy bruisability, gingival bleeding, epistaxis, mucosal bleedings of the gastrointestinal tract, profuse menstruations and prolonged bleeding after trauma, tonsillectomy, operation, delivery, or tooth extraction. In the most severe form of vWD the considerable decrease of factor VIII:C levels causes an additional defect of secondary haemostasis, which may